Patient Blood Management in intensive care patients

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Purpose of review
Patients admitted to ICUs are a heterogeneous group, displaying multiple anaemia risk factors and comorbidities. Clinicians should therefore take all possible measures to identify modifiable risks. Patient Blood Management (PBM) is an approach promoting the timely application of evidence-based interventions designed to maintain patients own blood mass.

Recent findings
Within ICU-patients, anaemia is highly prevalent. Generally, anaemia is associated with impaired outcome and need of blood transfusion. Currently, with ICUs working at full capacity and the global blood reserves exhausted, the SARS-CoV-2 pandemic reinforces the need for PBM implementation. For instance, implementation of a comprehensive coagulation management and measures to avoid iatrogenic blood loss may prevent bleeding-associated complications and adherence to blood transfusion guidelines may reduce adverse events associated with transfusion.

Summary
Critically ill patients display various morbidities often requiring individualized treatment. PBM offers patient-centred measures to improve outcome any time during hospital stay.

Keywords
anaemia, blood loss, ICU, Patient Blood Management

INTRODUCTION

According to the WHO, haemoglobin (Hb) levels of less than 12 g/dl in females and Hb less than 13 g/dl in males indicate anaemia [1]. At the time of admission to the ICU, up to two thirds of the patients suffer from anaemia [2,3,4▪]. Anaemia is associated with a reduced oxygen carrying capacity and affects up to 30% of the surgical patients [5,6,7▪▪,8▪]. Anaemia is mostly the result of an inadequate erythropoiesis due to iron deficiency, lack of vitamin B12 or folate, and bone marrow dysfunction. In the context of autoimmune diseases, acute, and chronic infections and/or cancer anaemia of inflammation can occur [9]. Here, increased hepcidin and reduced erythropoietin (EPO) levels lead to iron sequestration, decreased iron uptake and overall disturbed erythropoiesis. Overall, longer ICU treatment is positively correlated with the development of severe anaemia [10]. In addition, anaemia often persists in the first year after hospital discharge [4▪] and is an independent risk factor for morbidity and mortality [3,7▪▪,11▪,12–14].

Multiple factors cause or worsen a patients' degree of anaemia (Fig. 1) during ICU stay [15]. In addition to wound bleeding, ICU-admitted patients exhibit an increased risk for occult gastrointestinal bleeding. Here, especially patients with acute kidney injuries, chronic liver diseases, shock, and coagulopathies are at high risk [16]. Comprehensive coagulation management is therefore crucial to avoid unnecessary bleeding. In addition, ICU interventions, such as extracorporeal mechanical oxygenation (ECMO) or renal replacement therapy (RRT), induce physical stress and alter blood composition, which in turn trigger haemolysis and coagulation. Subsequent treatment with anticoagulation agents

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KEY POINTS

- Anaemia during ICU stay and after ICU discharge is associated with poor outcomes.
- PBM is a multimodal and multidisciplinary programme to treat anaemia, reduce blood loss, and apply rational, evidence-based blood transfusion policies.
- A large patient cohort benefits from implementation of PBM measures in ICUs.

however, increase the risk for bleeding, including occult gastrointestinal bleeding. In addition, patients admitted to the ICU after complex surgical procedures, trauma and/or medical conditions often require extensive monitoring of vital organ functions, leading to inevitable diagnostic blood losses. Subsequently, daily iatrogenic blood loss accumulates to significant blood volume loss throughout ICU stay [10].

Taken together, patients admitted to ICUs are a heterogeneous group, displaying various comorbidities. Therefore, it is crucial to develop individualized, patient-centred therapies. Historically, allogenic red blood cell (RBC) transfusions were the mainstay to increase Hb levels and correct anaemia. However, continually accumulating evidence suggests that blood transfusions themselves are predictors for increased morbidity and poor outcome, including mortality. Patient Blood Management (PBM) is a multimodal and multidisciplinary programme to treat anaemia, reduce blood loss, and apply rational, evidence-based blood transfusion policies. It comprises over 100 single measures, which facilitates its stepwise implementation adapted towards local conditions [17]. PBM implementation is associated with a decreased usage of RBC units, reduced complication and mortality rate [18–20]. Especially in the perioperative context, increasing evidence supports the implementation of PBM. In fact, perioperative PBM measures have major impact on ICU outcome and offer immense potential in improving the outcome of critically ill patients. However, also nonsurgical ICU-patients can benefit from PBM.

ANAEMIA MANAGEMENT IN INTENSIVE CARE PATIENTS

Particularly at ICU level, patients often display multiple anaemia risk factors in parallel. This results in a high frequency of iron deficiency anaemia and anaemia of inflammation. Among anaemia treatment and prevention options, iron supplementation and erythropoiesis-stimulating agents (ESA) are the most investigated ones. The benefits of preoperative iron supplementation in iron deficiency patients on perioperative outcome is widely accepted [21▪,22,23]. Triphaus *et al*. examined 1728 surgical patients. Preoperative intravenous iron

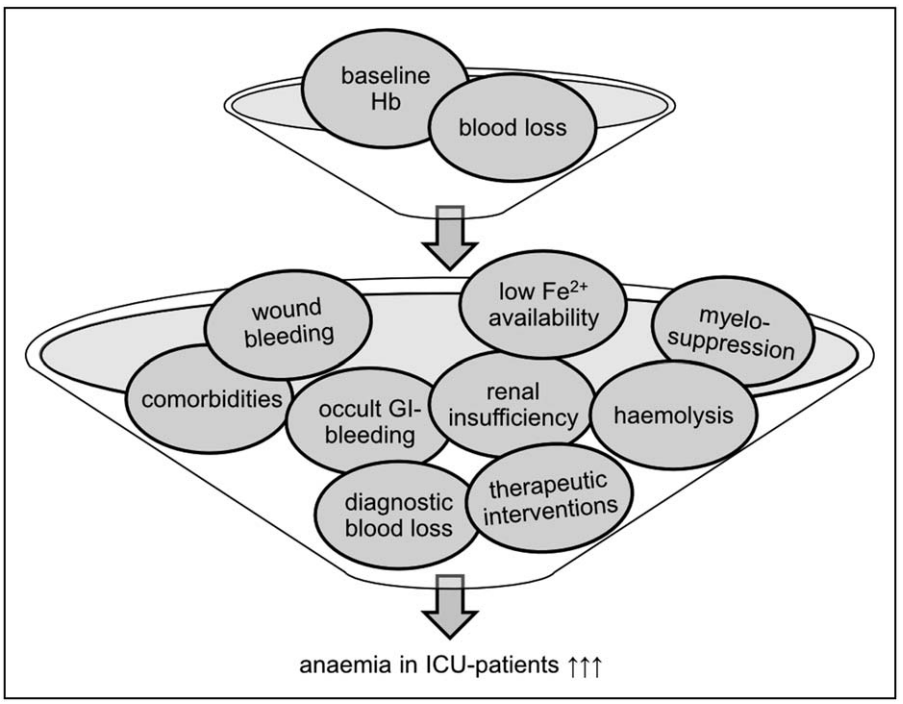

FIGURE 1. Multiple factors contribute to increased incidences of anaemia in ICUs. GI, gastrointestinal; Hb, haemoglobin.

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supplementation in iron deficiency patients resulted in a reduced administration of RBC units and a significant reduction in length of stay (LOS) (−2.8 days). Strikingly, intravenous iron supplementation more than 7 days before surgery decreased intraoperative RBC transfusions [21▪]. However, some studies question the benefits of preoperative iron supplementation [24▪,25▪]. The randomized controlled trial (RCT), PREVENTT examined 487 surgical patients treated with intravenous iron 10–42 days before surgery [24▪]. Here, the number of RBC transfusions (105 vs. 111, $P = 0.93$) was similar between the iron supplemented and placebo group. Furthermore, similar numbers of patients received at least one RBC transfusion or died within 30 days after surgery [iron-supplemented: 69/237 patients (29%) vs. placebo: 67/237 patients (28%)]. Limiting, as stated by the authors, is that preoperative iron deficiency was not tested before iron supplementation, thus the effect of intravenous iron was evaluated in patients without iron deficiency. Still, 30-day postoperative Hb values were increased in the treatment group, which suggests that perioperative iron supplementation increases Hb levels and aids recovery, particularly after surgery [24▪].

Due to the lack of evidence iron supplementation in ICU-patients is not generally recommended [26▪,27▪▪]. Currently, it is suggested in nonbleeding ICU-patients with iron deficiency and/or significant postoperative Hb reduction [28]. Shah *et al.* [29] conducted a meta-analysis including six RCTs comprising 805 ICU patients, and revealed that iron supplementation increased Hb levels (mean difference 0.3 g/dl). Litton *et al.* supplemented 140 iron deficiency patients with intravenous iron or placebo shortly after ICU admission. Here, the treated patients displayed increased Hb levels at the time of hospital discharge [30]. More recently, Kim *et al.* analysed the effect of iron supplementation in patients with acute postoperative anaemia (Hb < 7 g/dl). In total, 118 patients received iron or placebo shortly after total knee arthroplasty. Iron supplementation resulted in significantly higher levels of Hb, ferritin, iron, and transferrin saturation 2–12 weeks after surgery [31▪]. None of these RCTs detected a rise in adverse events or mortality upon intravenous iron administration.

To assess the safety and efficacy of ESA in adult ICU patients, Litton *et al.* [32] performed a meta-analysis and evaluated 21 studies, including 5452 patients. In-hospital mortality was lower in the treatment (12.6%) compared with the control group (15.4%). The relative risk (RR) for serious adverse events [1.11, confidence interval (CI) 0.94–1.31] and thromboembolic events (1.22, CI 0.95–1.58) was not significantly increased. Furthermore, Wijnberge *et al.* [33▪▪] performed a meta-analysis on the effect of ESA in 3387 ICU patients from eight RCTs. Here, a slight reduction in the proportion of transfused patients (RR 0.88, CI 0.78–1.00) and a small change in Hb (−0.31 g/dl, CI −0.51 to −0.05 g/dl) was found. In parallel, neither an increase in serious adverse events (RR 1.02, CI 0.9–1.15) nor in mortality (RR 0.8, CI 0.61–1.05) was found. Thus, intravenous iron and ESA seem to be safe in ICU patients with severe anaemia, and should be taken into account to optimize erythropoiesis.

PATIENT BLOOD MANAGEMENT MEASURES TO REDUCE ALLOGENEIC BLOOD TRANSFUSION

RBC transfusions at ICU level may be associated with increased morbidity and mortality, length of ICU stay and acute respiratory distress syndrome [3,34]. Hence, PBM aims to ensure guideline-adherent blood transfusion to improve patient outcome by the establishment of safe and evidence-based transfusion triggers. In general, different transfusion triggers are frequently observed [35]. A survey among 725 clinicians found low variability in the Hb threshold for the general ICU population (7 g/dl), whereas high variability was observed in patients on ECMO or with brain injuries (7–9 g/dl). A significant amount of evidence supports a restrictive transfusion strategy of Hb less than 7 g/dl in general, nonbleeding ICU patients [36], septic patients [37], and patients with gastrointestinal-bleeding [38]. Slightly higher restrictive Hb levels (Hb < 7–8 g/dl) are recommended in patients with cardiac diseases [39] or undergoing cardiac surgery [40] and patients with major burns [41]. In patients with acute neurological injuries [42] or patients requiring ECMO, beneficial transfusion triggers are still investigated. Several RCTs and meta-analyses published within the last 18 months and ongoing clinical trials evaluate and confirm benefits and safety of restrictive and liberal transfusion triggers in patient subgroups (Table 1).

PATIENT BLOOD MANAGEMENT SUPPORTS MEASURES FOR HAEMOSTASIS AND COAGULOPATHY

Ongoing bleeding is a common cause for anaemia in ICU patients. In acutely bleeding patients, it is crucial to control the source of bleeding, correct associated coagulopathies, and restore the blood volume. Coagulopathies can be induced by factors, such as hyperfibrinolysis, anticoagulation medications, plasma dilution, volume shifts, and

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Table 1. Recent randomized controlled trials, meta-analyses and ongoing studies analysing transfusion triggers in ICU patient subgroups published between December 2019 and May 2021

Reference	Study design	Patient population (sample size)	Transfusion trigger		Primary outcome and results
			Restrictive	Liberal	
General ICU					
Zhang *et al.* [43▪▪]	Meta-analysis	ICU patients (7 RCT, $n=7363$)	7 g/dl	9 g/dl	Restrictive transfusion is safe: ICU mortality (RR 0.82, 95% CI 0.62–1.08, $P=0.15$), 28/30-day mortality (RR 0.98, 95% CI 0.84–1.13, $P=0.74$), 60-day mortality (RR 1.01, 95% CI 0.87–1.16, $P=0.91$), 90-day mortality (RR 1.02, 95% CI 0.92–1.14, $P=0.69$), 120-day mortality (RR 1.29, 95% CI 0.67–2.47, $P=0.44$), and 180-day mortality (RR 0.91, 95% CI 0.75–1.12, $P=0.38$)
Sepsis					
TRANSfusion in Patients With Onco-hematological Malignancies ResusciTated From Septic Shock (TRANSPORT)	RCT	Malignant patients with septic shock	7 g/dl	9 g/dl	Ongoing (NCT03837171)
Acute coronary syndrome					
Ducrocq *et al.* [44▪]	RCT	Acute myocardial infarction ($n=668$)	8 g/dl	10 g/dl	Restrictive transfusion is safe: rate of major adverse cardiovascular events in restrictive [11% (95% CI, 7.5%–14.6%)] compared with liberal [14.0% (95% CI, 10.0%–17.9%)] transfusion
Gastrointestinal bleeding					
Kola *et al.* [45▪]	RCT	Acute upper GI bleeding ($n=224$)	7 g/dl	8 g/dl	Restrictive transfusion is safe: 45-day mortality upon restrictive (10/112 patients) and liberal (12/112 patients) transfusion ($P=0.65$)
Cardiac surgery					
Kashani *et al.* [46▪]	Systemic review meta-analysis	Cardiac surgery (10 RCT, $n=9101$)	7–8 g/dl, Hct 20–25%	8–10 g/dl, Hct 25–32%	Restrictive transfusion is safe based on the mortality risk (RR: 1.08; 95 CI: 0.76–1.54; $I^2=33\%$)
Acute neurological injury					
TRansfusion Strategies in Acute Brain INjured Patients (TRAIN)	RCT	Traumatic brain injury	7 g/dl	9 g/dl	Ongoing (NCT02968654)
HEMOglobin Transfusion Threshold in Traumatic Brain Injury OptimizatioN: The HEMOTION Trial (HEMOTION)	RCT	Traumatic brain injury	7 g/dl	10 g/dl	Ongoing (NCT03260478)
ECMO					
Doyle *et al.* [47▪]	Retrospective	ECMO ($n=402$)	8 g/dl	10 g/dl	Implementation of restrictive transfusion strategies is safe: ECMO survival (liberal 78.8% vs. restrictive 82.5%), ICU survival (73.7 vs. 78.2%) and 6-month survival (72.9 vs. 74.2%)

CI, confidence interval; ECMO, extracorporeal mechanical oxygenation; GI, gastrointestinal; Hct, hematocrit; RR, relative risk.

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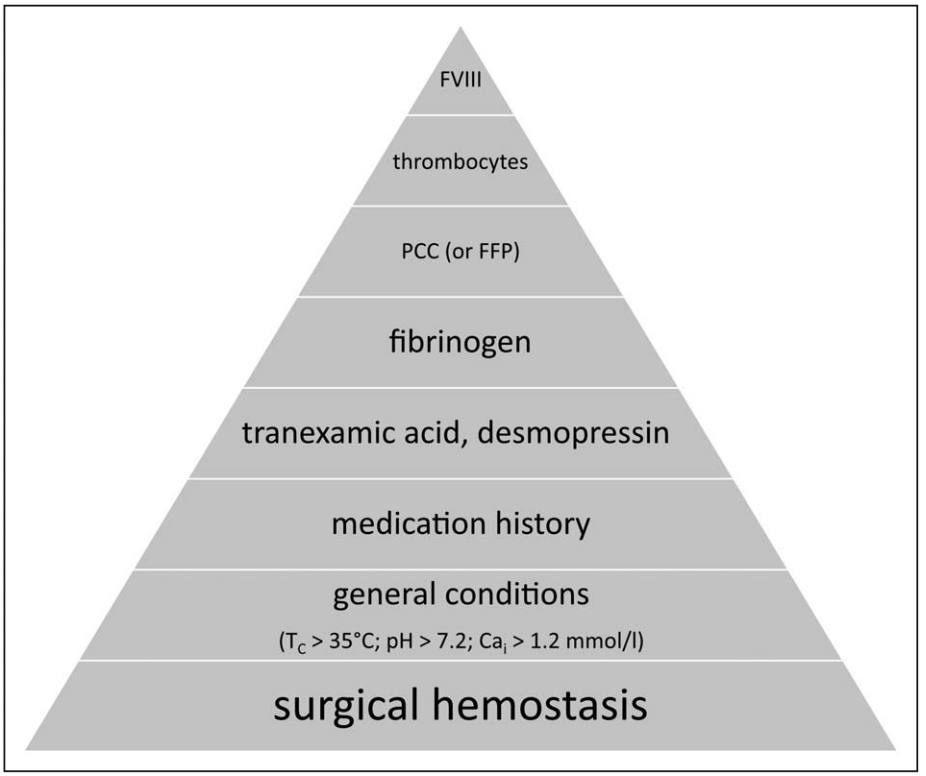

FIGURE 2. Optimized management of coagulopathy. Ca, calcium; FVIII, Factor VIII; FFP, fresh frozen plasma; PCC, prothrombin complex concentrate; T, temperature.

hypothermia. To generally aid coagulation, a balanced physiology is crucial. This includes maintaining body temperature above 35 °C (avoiding hypothermia), pH above 7.2 (avoiding acidosis) and ionized calcium over 1.0 mml/l (avoiding hypocalcaemia) [48]. Furthermore, implementation of algorithm-based coagulation treatment displayed the potential to reduce the use of blood products, ICU admissions, ventilation time and LOS (Fig. 2) [49,50].

Major bleeding caused by hyperfibrinolysis can be treated and prevented using tranexamic acid (TXA). In bleeding trauma patients or trauma patients with high risk of bleeding, TXA use is recommended as soon as possible after injury [51]. However, concerns remain about potential adverse events such as vascular occlusive events. To address this unsolved issue, TXA was evaluated in a recent meta-analysis by Taeuber *et al.* [52▪] including 218 trials comprising 125550 patients. Here, independent of dosing, TXA was not associated with an increased risk of thromboembolic events [52▪].

Further common in critical care is extracorporeal organ support, such as ECMO and RRT. These systems substantially increase the risk for thrombotic disorders and require the use of anticoagulation agents [53▪]. Widely applied anticoagulation agents, such as unfractioned heparin (UFH), low-molecular-weight heparin (LMWH), and direct thrombin inhibitors, share an increased risk for bleeding. However, for different patient subgroups, the most suitable anticoagulation treatment is still debated. In a retrospective study, Wilsey *et al.* [54▪] compared UFH with LMWH treatment after coronary artery bypass graft surgery. Though not significant, venous thromboembolism (2.12 vs. 1.41%) and bleeding (1.18 vs. 0.94%) occurred more frequently after UFH treatment compared with LMWH. Secondary endpoint analyses, revealed that the days mechanically ventilated, ICU and hospital LOS were significantly increased in the UFH cohort. In RCT including 638 critically ill patients requiring continuous RRT, regional citrate anticoagulation compared with systemic heparin was associated with a significantly increased filter life span (median 47 vs. 26 h) and showed an impressively lower risk of bleeding complications (odds ratio, 0.27; CI 0.15–0.49; $P < 0.001$) [55▪].

Besides physiological adaptations and medications, fast and reliable diagnostics are crucial in coagulation management. Bugaev *et al.* [56▪] compared the impact of point-of-care coagulation diagnostics [thromboelastography (TEG)/rotational thromboelastometry (ROTEM)] to standard diagnostics on treatment decisions. Their meta-analysis included 38 studies with more than 7400 patients.

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TEG/ROTEM usage reduced the number of transfused patients in acutely bleeding trauma patients (RR 0.74, CI 0.67–0.82), surgical (RR 0.83, CI 0.79–0.88) and critically ill patients (RR 0.83, CI 0.72–0.96).

PATIENT BLOOD MANAGEMENT MEASURES PREVENTING IATROGENIC BLOOD LOSS

Close observation of vital organ functions is crucial in ICU patients. However, excessive testing, together with its associated iatrogenic blood loss, is a major cause for hospital-acquired anaemia and subsequent requirement of RBCs [57▪▪,58▪▪]. Erythrocytes have a lifespan of about 120 days and the bone marrow produces 1% of the total blood volume (approx. 50 ml) every day. An analysis of 1894 cardiac surgery patients by Koch *et al.* [10] revealed a cumulative median phlebotomy volume of 332 ml [interquartile range (IQR) 197–619 ml] in ICU-admitted patients. For the entire hospitalization with a median LOS of 8 days, a median phlebotomy volume of 454 ml (IQR 270–813 ml) was estimated, which corresponds to the volume of 1–2 blood units. Strikingly, in patients with a LOS of 40–150 days, phlebotomy volumes between 2000 and 12500 ml were estimated. Similarly, based on 7273 ICU-patients, Jackson Chornenki *et al.* [57▪▪] estimated a median iatrogenic blood loss of 213 ml (IQR 133–382 ml). Bodley *et al.* [58▪▪] analysed 428 ICU-admitted patients and found a mean daily phlebotomy per patient of 48.1 ml and a maximal volume of 70 ml drawn on the first day. Consequently, it is not surprising that 40–50% of all ICU patients receive at least one RBC unit to compensate for the iatrogenic anaemia [10,57▪▪,58▪▪]. A straightforward approach to reduce iatrogenic blood loss is the switch to small volume phlebotomy tubes for diagnostic tests. Wu *et al.* [59▪▪] determined that the usage of small volume instead of standard tubes for routine laboratory tests reduced ICU blood loss by 22.9%. In addition, Bodley *et al.* [58▪▪] estimated, that due to the blood withdrawal procedure, daily iatrogenic blood loss comprises an estimate of 15 ± 8 ml wasted per patient. The implementation of closed-loop systems can reduce this volume by returning blood back into the patient instead of discarding. Riessen *et al.* [60] combined a closed-loop arterial blood sampling system, smaller tubes and reduced blood sampling frequencies in a before and after study. This approach resulted in a decreased daily iatrogenic blood loss from 43.3 to 15 ml. In addition to that, they measured a reduction from 7 to 2.3 RBC transfusions per 100 observation days and a decreased mean ICU LOS from 13 to 9.9 days.

PATIENT BLOOD MANAGEMENT DURING THE SARS-CoV-2 PANDEMIC

An advantage of PBM is the potential saving and preserving of blood reserves. Due to the SARS-CoV-2 pandemic, many ICUs are at full capacity, while the worldwide blood donations and reserves of blood products are severely limited. In this extreme situation, PBM offers solutions and addresses some of the challenges. Hence, PBM experts urge for immediate action [61,62▪]. Even the implementation of selected measures could save blood and increase patient safety at the same time.

Furthermore, anaemia as well as coagulopathies are prevalent in SARS-CoV-2 patients and can negatively affect outcomes. In a retrospective study, Bellmann-Weiler *et al.* [63▪] evaluated the prevalence of anaemia in 259 hospitalized SARS-CoV-2 patients. Upon admission, 24.7% displayed anaemia. Within the group of anaemic patients, about 68.8% suffered from anaemia of inflammation. During hospitalization, anaemia prevalence increased to 68.8% at day seven of admission. Overall, anaemia was associated with a longer hospitalization (9 vs. 12 days) and a higher in-hospital mortality (8 vs. 25%). Besides that, 88.2% of the patients displayed abnormal iron homeostasis at the time of hospital admission, of which the majority exhibited functional iron deficiency (79.3%).

In addition, several reports noted coagulation alterations in hospitalized SARS-CoV-2 patients, with increased prothrombin time and activated partial thromboplastin time compared with noninfected patients [64▪▪,65▪]. Subsequently, SARS-CoV-2 patients would likely benefit from comprehensive coagulation management for a timely, adapted treatment.

CONCLUSION

Critically ill patients are a heterogeneous group and often display various comorbidities. In addition, anaemia and coagulopathies are highly prevalent in critically ill patients. Anaemia and coagulopathies, but also allogeneic RBC transfusions are independent risk factors for complications and mortality. Therefore, particurlarly critically ill patients could immensely benefit from PBM measures facilitating blood saving, such as smaller phlebotomy volumes or closed-loop systems. In addition, increasing evidence supports the implementation of restrictive RBC transfusion strategies, not only in the perioperative setting, but also at ICU level. Furthermore, the management of haemostasis and coagulation offers potential to reduce anaemia prevalence and RBC requirements in ICU-patients.

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